DR. JACQUES ROUANET (Orcid ID : 0000-0002-5821-0786)

Article type : Letter to Editor

Recent outbreak of chilblain-like lesions is not directly related with SARS-CoV-2 infection

J. ROUANET[1], M.D., Ph.D,

E. LANG[1], M.D.,

F. BELTZUNG[2], M.D.,

B. EVRARD[3], M.D., Ph.D

C. HENQUELL[4], Pharm.D., Ph.D

I. JOULIE[1], M.D.,

M. D'INCAN, M.D., Ph.D [1],

[1]Department of Dermatology, CHU, Université Clermont Auvergne, 1 place Lucie et Raymond Aubrac, 63000 Clermont-Ferrand, FRANCE

[2]Department of Pathology, CHU, Université Clermont Auvergne, 1 place Lucie et Raymond Aubrac, 63000 Clermont-Ferrand, FRANCE

[3]Department of Immunology, CHU, Université Clermont Auvergne, 58, rue Montalembert, 63000 Clermont-Ferrand, FRANCE

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/JDV.16776

[4]Department of Virology, CHU, 3IHP, Université Clermont Auvergne, 58, rue Montalembert, 63000 Clermont-Ferrand, France

CORRESPONDING AUTHOR:

Dr Jacques ROUANET

Department of Dermatology, CHU Estaing,

1 place Lucie et Raymond Aubrac, 63000 Clermont-Ferrand, FRANCE

Tel: +33473755028

Mail: jrouanet@chu-clermontferrand.fr

WORD COUNT: 600/600; 1 Table, 1 Figure

Funding sources: None

Conflict of Interest Disclosures: None reported.

Throughout March and April 2020, dermatologists have observed an outbreak of chilblains despite climatic conditions not conducive to their apparition. These lesions have occurred simultaneously to the COVID-19 epidemic, suggesting a relationship between their onset and SARS-CoV-2 infection.

Here we describe a series of 10 patients presenting chilblain-like lesions in whom we have searched for evidence of SARS-CoV-2 infection.

Between April 17th and 29th 2020, we have included patients successively referred to our Department for chilblain-like lesions. Present and past medical history were recorded along with complete skin exam. Blood samples were collected for blood cell count, CRP, liver and renal parameters, antinuclear antibodies (anti-ENA and anti-DNA antibodies if positive immunofluorescence), complement components, ANCA, cryoglobulins, anti-prothrombinase, anticardiolipids, coagulation factors and D-dimers. Serological status concerning human immunodeficiency virus, hepatitis viruses and SARS-CoV-2 were established using automated assays performed on an Abbott ARCHITECT i2000 (Abbott Diagnostics). Two biopsies were performed on lesional skin for diagnosis by light microscope examination and for SARS-CoV-2 search by RT-PCR test targeting the RNA-dependent RNA polymerase gene (https://www.who.int/docs/default-source/coronaviruse/real-time-rt-pcr-assays-for-the-detection-of-sars-cov-2-institut-pasteur-paris.pdf). We also searched for SARS-CoV-2 on a nasopharyngeal swab using RT-PCR.

Ten patients were included (median age: 33 years (11-57), sex-ratio 1:1). All had erythematous, livedoid and purplish patches and papules on fingers or toes, evolving towards erosions, pigmentation and scaling (Figure, Table). In eight patients, lesions began with a burning pain, which shifted towards pruritus in five patients. Lesions started 26.5 days prior to consultation (14-52) and healed within 35 days (27-45) without sequelae in 7 patients. Five patients experienced short-duration viral symptoms without fever, anosmia nor ageusia. None of them had contact with a confirmed COVID infected person. Biopsies showed (Figure) inconstant epidermal lesions (apoptotic keratinocytes, epidermal necrosis, basal layer vacuolation, mild spongiosis and parakeratosis), an upper dermis edema, and a perivascular and periadnexal lymphohistiocytic infiltrate. Vascular lesions were prominent with angiocentrism, angiotropism and endothelium swelling, capillar ectasy and fibrinoid thrombi. All blood sample examinations were normal except for three patients who had positive antinuclear antibodies with anti-nucleolar or anti-centromere

patterns. SARS-CoV-2 research on nasopharyngeal swabs and on skin biopsies was negative and no SARS-CoV-2 specific IgG were detected in any case.

We present a series of 10 consecutive patients with typical clinical and pathological chilblains occurring during the peak of COVID-19 infection. In our area, the weather was warm at that time and all patients lived under lockdown in well-heated houses. In all patients, we failed to demonstrate neither a current nor recent COVID-19 infection nor SARS-CoV-2 presence in skin. The absence of respiratory symptoms and the known rapid clearance of SARS-CoV-2 in moderate infections could explain the negativity of RT-PCR analysis. The absence of specific IgG suggests that a reaction due to COVID-19 is unlikely even though these patients could have only specific IgM. However, IgM peak between days 5 and 12 after infection[1] whereas IgG reach peak concentrations after day 20 and most patients were tested after 20 days of evolution of skin lesions. Furthermore, the sensitivity[2] of our test is 100% after day 17. Three of these patients had positive antinuclear antibodies suggesting an undiagnosed autoimmune disease (scleroderma or lupus) but no one presented other clinical symptoms.

Chilblain-like lesions have been reported for several weeks[3-5] in patients COVID infected or not, suggesting that they could be induced by SARS-CoV-2. Our data do not confirm a direct role of SARS-CoV-2 or an immunological hit-and-run mechanism. Some of these patients might have an authentic systemic disease, fortuitously detected. To conclude, our results do not support a direct effect of SARS-CoV-2 in the observed outbreak of unusual chilblain lesions during the COVID-19 pandemic.

Acknowledgement: The patients in this manuscript have given written informed consent to the publication of their case details. We thank Dr Elodie DEVERS (Department of Dermatology), Dr Carole CHEVENET (Department of Pathology), Dr Anne-Sophie MARCHESSEAU-MERLIN, Dr François MICHEL and Dr Charlotte PIECH, (dermatologists), Pr Marc BERGER and Dr Juliette BERGER (CRB-Auvergne), Pr Marc RUIVARD (Department of Internal Medicine) and Matthieu GEMBARA (manuscript proofreading).

Author Contributions: Dr Rouanet had full access to all of the data of the case series and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Rouanet, D'Incan.

Critical revision of the manuscript for important intellectual content: All authors.

Supervision: Rouanet, D'Incan.

Conflict of Interest Disclosures: None reported.

REFERENCES

[1] Kontou PI, Braliou GG, Dimou NL, Nikolopoulos G, Bagos PG. Antibody Tests in Detecting SARS-CoV-2 Infection: A Meta-Analysis. Diagnostics (Basel). 2020;10; 319.

[2] Bryan A, Pepper G, Wener MH, Fink SL, Morishima C, Chaudhary A, et al. Performance Characteristics of the Abbott Architect SARS-CoV-2 IgG Assay and Seroprevalence in Boise, Idaho. J Clin Microbiol. 2020.In press.

[3] de Masson A, Bouaziz JD, Sulimovic L, Cassius C, Jachiet M, Ionescu MA, et al. Chilblains are a common cutaneous finding during the COVID-19 pandemic: a retrospective nationwide study from France. J Am Acad Dermatol. 2020. In press.

[4] Galvan Casas C, Catala A, Carretero Hernandez G, Rodriguez-Jimenez P, Fernandez Nieto D, Rodriguez-Villa Lario A, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. 2020. In press.

[5] Piccolo V, Neri I, Filippeschi C, Oranges T, Argenziano G, Battarra VC, et al. Chilblain-like lesions during COVID-19 epidemic: a preliminary study on 63 patients. J Eur Acad Dermatol Venereol. 2020. In press.

FIGURE LEGEND

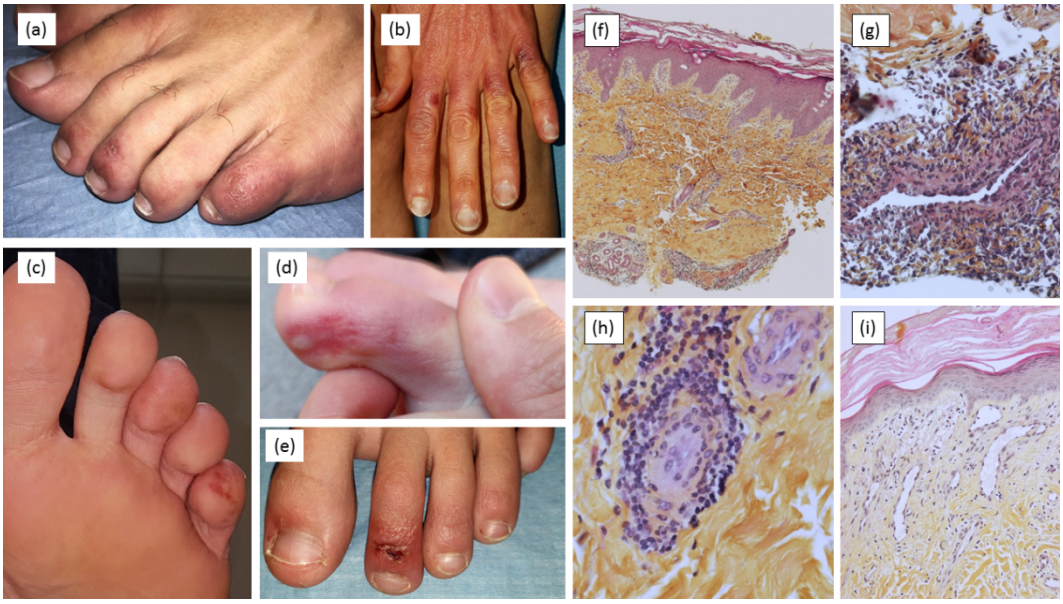
Figure - Skin lesions (*a: Patient 7; b: Patient 9; c: Patient 10; d: Patient 4; e: Patient 3;)* ; **Lesional skin biopsies, Hematoxylin, Eosin and Saffron (HES) (***f: lympho-histiocytic infiltrate around vessels and eccrine glands, x4 magnification; g: Angiocentric lympho-histiocytic infiltrate in superficial dermis, x40 magnification; h: Angiotropism, x40 magnification; i: Papillar oedema, capillar ectasy and endothelial swelling, x20 magnification)*

TABLE

Table 1- Patient characteristics

	MEDICAL HISTORY					CLINICAL EXAMINATION		BIOLOGY		SARS-COV-2 PCR	
PATIENT	**Age/ Sex**	**Relevant past medical history**	**Associated viral symptoms**	**Time between 1st symptoms and consultation (days)**	**Skin symptoms duration to healing (days)**	**Clinical description**	**Topography**	**Antinuclear antibodies (titer)**	**SARS-CoV-2 serological status**	**Naso-pharyngeal swab**	**Skin biopsy**
1	60/F	Raynaud's disease	None	28	38	Purplish macule	Right index fingertip	Negative	Negative	/	Negative
2	32/H	/	Asthenia	25	35	Erythematous and purplish patches and -papules with superficial erosion	Dorsal side of the toes (right I, III, IV,V and left I, II, IV, V)	Negative	Negative	Negative	Negative
3	11/H	/	Asthenia, headaches	28	27	Erythematous purplish patches and -papules with superficial erosion and post-inflammatory scaling	Dorsal surface of the toes (both side I and II)	Negative	Negative	/	Negative
4	18/H	/	None	16	27	Erythematous, liveoid and purplish purplish patches and -papules with superficial erosion	Dorsal and lateral sides of the toes (left I, II, III, V) and fingers	Positive (1/640) *anti-centromere antibodies*	Negative	Negative	Negative
5	34/F	Raynaud's disease, chilblains	None	52	> 60	Purplish and livedoïd macules with post-inflammatory scaling	Dorsal side and fingertips of the all toes	Positive (1/2560) *nucleolar fluorescence*	/	Negative	Negative
6	57/F	/	None	14	> 60	Purplish macules	All fingertips	Positive (1/160) *dense cytoplasmic fluorescence*	Negative	/	Negative
7	24/H	/	None	22	29	Erythematous and purplish patches and -papules with superficial erosion and post-inflammatory scaling	Dorsal side of the toes (right III, IV, V and left II, IV, V)	Negative	Negative	Negative	/
8	50/F	/	Asthenia	37	45	Purplish and livedoïd patches	Toe fingertips (left I, II, III)	Negative	Negative	Negative	Negative

	MEDICAL HISTORY					CLINICAL EXAMINATION		BIOLOGY		SARS-CoV-2 PCR	
PATIENT	**Age/ Sex**	**Relevant past medical history**	**Associated viral symptoms**	**Time between 1st symptoms and consultation (days)**	**Skin symptoms duration to healing (days)**	**Clinical description**	**Topography**	**Antinuclear antibodies (titer)**	**SARS-CoV-2 serological status**	**Naso-pharyngeal swab**	**Skin biopsy**
9	40/F	Raynaud's disease, chilblains	Headaches	24	> 60	Erythematous patches with post-inflammatory scaling	Dorsal side of the fingers with respect of the interphalangeal joints (right II, III, IV, V and left II, III, IV, V)	Negative	Negative	Negative	Negative
10	14/H	/	Cough, asthenia, headaches, myalgia, arthralgia	35	43	Erythematous, liveoid and purplish purplish patches and -papules with post-inflammatory pigmentation and scaling	Dorsal surface and fingertips of all toes	Negative	Negative	Negative	Negative



jdv_16776_f1.tif